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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,666	11/15/2001	David Botstein	P2730P1C42	4941
35489	7590	09/15/2006		EXAMINER
HELLER EHRLICH LLP 275 MIDDLEFIELD ROAD MENLO PARK, CA 94025-3506			DEBERRY, REGINA M	
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 09/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,666	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 05 July 2006.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 121-127 and 129-131 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) 124-127 and 129-131 is/are allowed.
- 6) Claim(s) 121-123 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>7/06</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission filed on 05 July 2006 has been entered.

Status of Application, Amendments and/or Claims

Applicant's arguments filed 05 July 2006 have been entered in full. The Polakis Declaration (Exhibits A and B) filed on 05 July 2006 under 37 CFR 1.132 has been entered. Claims 121-127, 129-131 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The information disclosure statement(s)(IDS) filed 05 July 2006 was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

Withdrawn Objections And/Or Rejections

The rejection to claims 121-127 and 129-131 under 35 U.S.C. 101, as set forth at pages 2-5 of the previous Office Action (10 January 2006), is *withdrawn* in view of Applicant's arguments (05 July 2006). The Polakis Declaration (Exhibits A and B) under 37 CFR 1.132 filed 05 July 2006 is sufficient to overcome the rejection of claims 121-127 and 129-131 based upon 35 U.S.C. 101.

The rejection to claims 121-127 and 129-131 under 35 U.S.C. 112, First Paragraph, Enablement, as set forth at page 5 of the previous Office Action (10 January 2006), is *withdrawn* in view of Applicant's arguments (05 July 2006). The Polakis Declaration (Exhibits A and B) under 37 CFR 1.132 filed 05 July 2006 is sufficient to overcome the rejection of claims 121-127 and 129-131 based upon 35 U.S.C. 112, First Paragraph, Enablement.

35 US § 112, First Paragraph, Written Description

Claims 121-123 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth at pages 5-9 of the previous Office Action (10 January 2006)..

Applicant discusses the legal test for written description and various case law. Applicant states that the Examiner directed Applicant's attention to Example 14 of the Synopsis of Application of Written Description Guidelines. Applicant argues that the

guidelines state that the protein variants meet the requirement of 35 U.S.C. 112, first paragraph, as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if the procedures for making such variants is routine in the art, the specification provides an assay for detecting the functional activity of the protein and the variant proteins possess the specified functional activity and at least 95% sequence identity to the reference sequence. Applicant argues that the instant claims recite a specific functional limitation that the nucleic acid encoding the native sequence polypeptides are overexpressed in lung or colon tumors. Applicant argues that Example 170 in the instant specification, sets forth a gene amplification method and provides step-by-step guidelines and protocols for gene amplification assays for determining whether a gene which encodes for the native polypeptide having at least 90% identity to PRO1185 is overexpressed in lung or colon tumors. Applicant points to the specification's disclosure of methods for the determination of percent identity, and assays for identification of nucleic acids and for support of the functional limitation in the claims. Applicant urges that the skilled artisan can readily test native polypeptide sequences for identity and whether or not the encoding nucleic acids are amplified in tumors.

Applicant's arguments have been fully considered but are not found to be persuasive. The fact pattern in the instant application is not analogous to Example 14 in the Revised Interim Written Description Guidelines. In Example 14 of the Guidelines, the claimed protein variants have a high percent sequence identity in combination with a specific functional limitation. In the example, the protein catalyzes the reaction of A→B

and thus, methods of generating variants of the protein that have 95% identity and retain its activity are conventional in the art because deletions, substitutions, insertions, and additions of uncritical amino acid residues would not affect the enzyme activity. Moreover, such an enzyme would have a conserved structure that is responsible for the enzyme activity. Thus, it is likely predictable, based upon percent identity, which variant would share the same function. The instant specification contemplates but does not exemplify variants of the protein wherein the variant can have any number of substitutions, deletions, insertions and/or additions in SEQ ID NO:401, wherein said nucleic acid encoding said polypeptide is overexpressed in lung or colon tumor cells. The specification and the claims do not disclose the identification of any particular portion of the PRO1185 structure that must be conserved in order to conserve the required function. Applicant has not described, shown possession of or described a representative number of species of polypeptides 90%, 95%, and 99% homologous to SEQ ID NO:401, that still retain the function of SEQ ID NO:401. The specification of the instant application only teaches a PRO1185 polypeptide of SEQ ID NO:401. The description of one PRO1185 polypeptide species (SEQ ID NO:401), **which is not a member of a known family of proteins**, is not adequate written description of an entire genus of functionally equivalent polypeptides which incorporate all variants, fragments, and derivatives wherein the nucleic acid encoding the protein is overexpressed in lung tumor cells. A method of calculating the percentage identity is not equivalent to a method of making and it does not provide description for the instantly claimed genus of PRO1185 polypeptide variants. The courts have specifically stated

that the skilled artisan cannot envision the *detailed chemical structure* of an encompassed polypeptide until the structure is disclosed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. In the instant case, SEQ ID NO:401 has been disclosed, but no native sequence variants thereof have been disclosed regardless of whether or not they are encoded by nucleic acids that are amplified in tumors. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factors present in the claims are a partial structure in the form of a recitation of percent identity, a requirement that the sequence be native, and a requirement that the encoding nucleic acids are amplified in lung and colon tumors. There is no identification of any particular portion of the structure that must be conserved in order to conserve the required function.

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Additionally, there is the issue of whether or not the single disclosed embodiment is actually amplified in lung or colon tumors (see maintained rejections under 35 U.S.C. §§ 101 and 112, first paragraph, above). Clearly, such does not constitute disclosure of a representative number of examples of, nor adequate written description for, the claimed genus. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

35 U.S.C. § 112, First Paragraph, Scope of Enablement

Claims 121-123 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

"an isolated native sequence polypeptide comprising the amino acid sequence of SEQ ID NO:401...",

does not reasonably provide enablement for:

an isolated native sequence polypeptide having at least 90%, 95% or 99% amino acid sequence identity to SEQ ID NO:401...".

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification states that amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers and diagnostic determination of the presence of those cancers (page 539, lines 20-25). The specification teaches experiments to determine

whether the DNA encoding the PRO polypeptide is over-represented in any of the primary lung, colon cancers or breast cancer cell line that were screened. The results of the TaqMan are reported in deltaCt units. One unit corresponds to 1 PCR cycle or approximately a 2-fold amplification relative to normal (page 539, lines 26-41). The specification teaches that primary tumor (human lung tumor) LT3, LT26 and LT30 have deltaCt units of 1.01, 1.66 and 1.58 respectively for PRO1185 (page 552). The specification teaches that human colon cancer CT2 has a deltaCt unit of 1.73 for PRO1185 (page 552).

There is no guidance in the specification, in the working examples or in the art of record showing what variant sequence is overexpressed in the tumors. Thus, if one skilled in the art were to make diagnostic probes (e.g. labeled antibody or protein) from the claimed variants, there is no guidance regarding what changes can be made without loss of probe specificity. The instant specification contemplates but does not exemplify variants of the protein wherein the variant can have any number of substitutions, deletions, insertions and/or additions in SEQ ID NO:401, wherein said nucleic acid encoding said polypeptide is overexpressed in lung or colon tumor cells. In addition, as is well recognized in the art, any modification (even a "conservative" substitution) to a critical structural region of a protein is likely to significantly alter its functional properties. It is known for nucleic acids as well as proteins, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases (Wells, 1990, Biochemistry 29:8509-8517, reference of record). Thus, the instant claims would not be enabled because the specification fails to teach how to make variant

sequences of SEQ ID NO:401, which could be used in cancer treatment (e.g. antagonist or agonist).

As was stated in the previous Office Action (22 March 2004, page 7), there are no working examples of polypeptide sequences less than 100% identical to SEQ ID NO:401, thus the skilled artisan would not know how to use non-identical sequences on the basis of the teachings in the specification unless they possessed some sort of function, which the specification fails to teach. The specification does not provide any guidance as to what changes should be made and which regions of the instant protein are functionally and structurally critical.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

Claims 121-123 are rejected.

Claims 124-127 and 129-131 are allowed.

This is a continuation of applicant's earlier application. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


RMD
9/12/06

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